SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Palladone SR 24mg prolonged-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains hydromorphone hydrochloride 24 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule.

Hard gelatin capsule containing spherical prolonged release pellets. PALLADONE-SR capsules 24 mg are dark blue/clear capsules marked HCR24.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in cancer.
PALLADONE-SR capsules are indicated in adults and children aged 12 years and above.

4.2 Posology and method of administration

Posology
Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with hydromorphone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Transferring patients between oral and parenteral hydromorphone
Switching patients from parental hydromorphone to oral hydromorphone should be guided by the sensitivity of the individual patient. The oral starting dose should not be overestimated (for oral bioavailability see section 5.2).

Adults and children aged 12 years and above
Palladone SR capsules should be used at 12 hourly intervals. The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. 4 mg of hydromorphone has an efficacy approximately

equivalent to 30 mg of morphine sulphate given orally. A patient presenting with severe pain should normally be started on a dosage of 4 mg ***Palladone SR*** capsules 12 hourly. Increasing severity of pain may require increased dosage of hydromorphone to achieve the desired relief.

Elderly and patients with renal impairment
The elderly and patients with renal impairment should be dose titrated with ***Palladone SR*** capsules in order to achieve adequate analgesia. It should be noted, however, that these patients may require a lower dosage to achieve adequate analgesia.

Patients with hepatic impairment
Contraindicated.

Paediatric population.
Not recommended.

Method of administration
For oral use.
The capsules can be swallowed whole or opened and their contents sprinkled on to cold soft food.

4.3 Contraindications

Hydromorphone is contra-indicated in patients with:

- Known hypersensitivity to hydromorphone or any of the excipients
- Severe respiratory depression with hypoxia and/or hypercapnia
- Severe chronic obstructive lung disease
- Severe bronchial asthma
- Paralytic ileus
- Acute abdomen
- Coma
- Hepatic impairment
- Concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation

4.4 Special warnings and precautions for use

Hydromorphone should be administered with caution in the debilitated elderly and in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin

- Hypotension with hypovolaemia
- Pancreatitis
- Hypothyroidism
- Toxic psychosis
- Prostatic hypertrophy
- Adrenocortical insufficiency (e.g., Addison's disease)
- Severely impaired renal function
- Severely impaired hepatic function
- Alcoholism
- Delirium tremens
- Convulsive disorders
- Constipation
- Shock or reduced respiratory reserve.

Respiratory depression
The major risk of opioid excess is respiratory depression.

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Risk from concomitant use of sedative medicines such as benzodiazepines (and other CNS depressants):
Concomitant use of ***Palladone SR*** capsules and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe ***Palladone SR*** capsules concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep□related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent manner (see section 4.8).
In patients who present with CSA, consider decreasing the total opioid dosage

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids.

Abuse or intentional misuse of ***Palladone SR*** may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.***Palladone SR*** capsules are not recommended for pre-operative use or in the first 24 hours post-operatively. After this time they should be used with caution, particularly following abdominal surgery.

Palladone SR capsules should not be used where there is the possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Palladone SR*** capsules should be discontinued.

Patients about to undergo cordotomy or other pain relieving surgical procedures should not receive ***Palladone SR*** capsules for 24 hours prior to surgery. If further treatment with ***Palladone SR*** capsules is indicated then the dosage should be adjusted to the new post-operative requirement.

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with hydromorphone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including

irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

The prolonged release capsules may be opened and their contents sprinkled onto soft cold food.

The content (pellets) of the prolonged release capsules must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed hydromorphone pellets leads to a rapid release and absorption of a potentially fatal dose of hydromorphone (see section 4.9).

Concomitant use of alcohol and ***Palladone SR*** capsules may increase the undesirable effects of ***Palladone SR*** capsules; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Opioids, such as hydromorphone, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system (CNS):
The concomitant use of opioids with sedative medicines such as benzodiazepines or other drugs that depress the CNS increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of concomitant use should be limited (see section 4.4). Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics and sedatives (including benzodiazepines), anaesthetics (e.g. barbiturates), antiemetics, antidepressants, antipsychotics (e.g. phenothiazines), antihistamines and alcohol.

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Co-administration with monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use is contraindicated (see section 4.3).

Alcohol may enhance the pharmacodynamic effects of ***Palladone SR*** capsules; concomitant use should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no well-controlled studies of hydromorphone in pregnant women. Hydromorphone should not be used in pregnancy unless clearly necessary. ***Palladone SR*** capsules are not recommended during pregnancy and labour due to impaired uterine contractility. Regular use in pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as hydromorphone is excreted into breast milk in low amounts and may cause respiratory depression in the infant.

Fertility

Non clinical toxicology studies in rats have not shown any effects on male or female fertility or sperm parameters.

4.7 Effects on ability to drive and use machines

Hydromorphone may cause drowsiness and patients should not drive or operate machinery if affected.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - The medicine has been prescribed to treat a medical or dental problem; and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

Hydromorphone may cause constipation, nausea and vomiting. Constipation may be treated with appropriate laxatives. When nausea and vomiting are troublesome ***Palladone SR*** capsules can be readily combined with antiemetics.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Not known	Cannot be estimated from the available data

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders						Hypersensitivity (including oropharyngeal swelling); Anaphylactic reactions
Metabolism and nutrition disorders		Decreased appetite				
Psychiatric disorders		Confusional state; Anxiety; Insomnia	Agitation; Depression; Euphoric mood; Hallucinations; Nightmares			Drug dependence (see section 4.4); Dysphoria
Nervous system disorders	Dizziness; Somnolence	Headache	Myoclonus; Tremor; Paraesthesia	Sedation; Lethargy		Convulsions; Dyskinesia; Hyperalgesia (see section 4.4); Central sleep apnoea syndrome
Eye disorders			Visual impairment			Miosis
Cardiac disorders				Tachycardia		

	Very common	Common	Uncommon	Rare	Very rare	Not known
Vascular disorders			Hypotension			Flushing
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Respiratory depression		
Gastrointestinal disorders	Constipation; Nausea	Abdominal pain; Dry mouth; Vomiting	Diarrhoea; Dysgeusia			Paralytic ileus
Hepatobiliary disorders			Hepatic enzymes increased			
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis	Rash			Urticaria
Renal and urinary disorders			Urinary retention			
Reproductive system and breast disorders			Erectile dysfunction			
General disorders and administration site conditions		Asthenia	Drug withdrawal syndrome; Fatigue; Malaise; Peripheral oedema			Drug tolerance; Drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs of hydromorphone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, pneumonia aspiration, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases. Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage.

Toxic leukoencephalopathy has been observed with hydromorphone overdose.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Treatment of overdosage:
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children), if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state.

Intramuscular naloxone is an alternative in the event IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on hydromorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Other supportive measures as indicated by the patient's progress and clinical condition should be considered.

Additional/other considerations:
Consider activated charcoal (50 g for adults, 1g/kg for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.

Palladone SR capsules will continue to release and add to the hydromorphone load for up to 12 hours after administration and management of hydromorphone overdosage should be monitored accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

SUMMARY OF PRODUCT CHARACTERISTICS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid
ATC code: N02A A03

Like morphine, hydromorphone is an agonist of mu receptors. The pharmacological actions of hydromorphone and morphine do not differ significantly. The oral analgesic potency ratio of hydromorphone to morphine is approximately 5-10:1. Hydromorphone and related opioids produce their major effects on the central nervous system and bowel. The effects are diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and alteration of the endocrine and autonomic nervous system.

Endocrine system
See section 4.4.

Other pharmacological effects
In vitro and preclinical studies indicate various effects of natural opioids, such as morphine, on components of the immune system: the clinical significance of these findings is unknown. Whether hydromorphone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Absorption:
Hydromorphone is absorbed from the gastrointestinal tract and undergoes pre-systemic elimination resulting in an oral bioavailability of about 32%.

Distribution
Plasma protein binding of hydromorphone is low (< 10 %). This percentage remains constant up to very high plasma levels of approximately 80 ng/ml, which are only very rarely achieved with very high hydromorphone doses.

Metabolism
Hydromorphone is metabolised by direct conjugation or reduction of the keto group with subsequent conjugation. Hydromorphone is primarily metabolised to hydromorphone-3-glucuronide, hydromorphone-3-glucoside and dihydroisomorphine-6-glucuronide. Smaller portions of the metabolites dihydroisomorphine-6-glucoside, dihydromorphine and dihydroisomorphine have also been found. Hydromorphone is metabolised via the liver; a smaller portion is excreted unchanged via the kidneys.

Elimination
Hydromorphone metabolites were found in plasma, urine and human hepatocyte test systems. There are no indications to hydromorphone being metabolised in vivo via the cytochrome P 450 enzyme system. In vitro, hydromorphone has but a minor inhibition effect (IC50 > 50 μM) on recombinant CYP isoforms, including CYP1A2, 2A6, 2C8, 2D6 und 3A4.

Hydromorphone is therefore not expected to inhibit the metabolism of other active substances which metabolise via these CYP isoforms.

5.3 Preclinical safety data

Carcinogenicity
Hydromorphone was non-genotoxic in a bacterial mutation test, in the in vitro human lymphocyte chromosome aberration assay and the in vivo mouse micronucleus assay but positive in the mouse lymphoma assay with metabolic activation. Similar findings have been reported with other opioid analgesics. Long term carcinogenicity studies have not been performed.

Reproductive toxicity
No effects have been observed on male or female fertility or sperm parameters in rats.

Hydromorphone was not teratogenic in pregnant rats nor rabbits given oral doses during the major period of organ development. Evidence of a teratogenic effect in mice and hamsters has been reported in the literature.

In a rat pre- and post-natal study, there was an increase in pup mortality and reduced body weight gain in the early postnatal period, associated with maternal toxicity. No effects on continued pup development or reproductive performance were observed.

6.1 List of excipients

Microcrystalline cellulose
Hypromellose
Ethylcellulose (N10)
Colloidal anhydrous silica
Dibutyl sebacate

Capsule shells
Gelatin
Sodium laurilsulfate
Indigo carmine (E132)
Titanium dioxide (E171)

Black printing ink
Shellac
Propylene glycol
Iron oxide (E172)

6.2. Incompatibilities

None known.

6.3. Shelf Life

Eighteen months.

6.4. Special Precautions for Storage

Do not store above 25°C. Store in the original package.

6.5. Nature and Contents of Container

a) PVdC/PVC blister packs with aluminium backing foil.
b) Polypropylene containers with polyethylene lids.

Pack sizes: 30, 56, 60 capsules.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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